

# PATENT SPECIFICATION

(11) 1 460 348

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- (21) Application No. 5015/74 (22) Filed 4 Feb. 1974  
 (61) Patent of Addition to No. 1 356 834 dated 27 Sept. 1972  
 (23) Complete Specification filed 2 Jan. 1975  
 (44) Complete Specification published 6 Jan. 1977  
 (51) INT CL<sup>2</sup> C07D 403/04; A61K 31/505; C07C 91/04 //  
 (C07D 403/04, 209/04, 239/95)  
 (52) Index at acceptance  
 C2C 1343 1604 213 220 22Y 246 247 250 251 252 25Y  
 28X 305 30Y 327 364 366 367 368 36Y 373 37Y  
 464 552 614 628 658 65X 667 672 677 744 758  
 790 79Y QS RR  
 A5B 244 246 24Y 275 27Y 294 29Y 381 38Y 392 39X 441  
 44Y 480 482 48Y 504 50Y 551 552 55Y 575 576  
 57Y 616 61Y 670 67Y 77Y

(72) Inventors GEORGE RICHARD BIRCHALL, WALTER  
 HEPWORTH and STEPHEN COLLYER SMITH



## (54) QUINAZOLINE DERIVATIVES

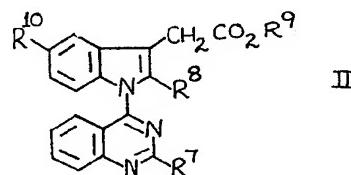
(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, Imperial Chemical House, Millbank, London, SW1P 3JF, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new quinazoline derivatives which possess anti-inflammatory and analgesic activity, and it is an improvement in or modification of the invention described in cognate United Kingdom patent application Nos. 51086/71, 18116/72 and 30767/72 (Serial No. 1,356,834).

In the above Patent specification there are described compounds of the formula:

covered that such compounds possess useful anti-inflammatory and analgesic activity.

According to the invention there is provided a compound of the formula:—



wherein R<sup>7</sup> is a C<sub>1-3</sub>-alkylthio radical, R<sup>8</sup> is hydrogen or a methyl radical, R<sup>9</sup> is hydrogen or a C<sub>1-3</sub>-alkyl radical, and R<sup>10</sup> is hydrogen,

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## ERRATA

SPECIFICATION No. 1,460,348

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Page 4, line 79, for syrup read syrupy  
 Page 6, line 1, delete whole line insert wherein  
 R<sup>7</sup> and R<sup>10</sup> have the meanings stated

THE PATENT OFFICE  
 5th August, 1977

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30 pounds wherein K<sup>4</sup> is a quinazolin-4-yl radical  
 bearing an alkylthio radical in the 2-position  
 of the quinazoline nucleus. We have now dis-

for example, 5 - methoxy - 2 - methyl - 1 -  
 (2 - methylthioquinazolin - 4 - yl) - indol -  
 3 - ylactic acid, 5 - methoxy - 2 - methyl -

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 A5B 244 246 24Y 275 27Y 294 29Y 381 38Y 392 39X 441  
 44Y 480 482 48Y 504 50Y 551 552 55Y 575 576  
 57Y 616 61Y 670 67Y 77Y

(72) Inventors **GEORGE RICHARD BIRCHALL, WALTER HEPWORTH and STEPHEN COLLYER SMITH**

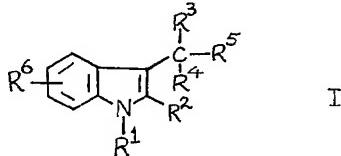


## (54) QUINAZOLINE DERIVATIVES

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In the above Patent specification there are described compounds of the formula:—

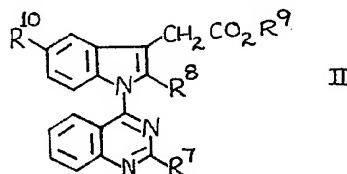


wherein, among others, R<sup>1</sup> is a quinazolin-4-yl radical bearing a C<sub>1-5</sub>-alkylthio radical, R<sup>2</sup> is hydrogen or a methyl radical, R<sup>3</sup> and R<sup>4</sup> are hydrogen, R<sup>5</sup> is a radical of the formula —COR<sup>7</sup> wherein R<sup>7</sup> is a hydroxy or C<sub>1-5</sub>-alkoxy radical, and R<sup>6</sup> is hydrogen or a C<sub>1-5</sub>-alkoxy or C<sub>1-5</sub>-alkyl radical or a halogen atom, and the pharmaceutically-acceptable salts thereof.

However there is no specific example of a compound wherein R<sup>1</sup> is substituted by an alkylthio radical and no disclosure of any compounds wherein R<sup>1</sup> is a quinazolin-4-yl radical bearing an alkylthio radical in the 2-position of the quinazoline nucleus. We have now dis-

covered that such compounds possess useful anti-inflammatory and analgesic activity.

According to the invention there is provided a compound of the formula:—



wherein R<sup>7</sup> is a C<sub>1-3</sub>-alkylthio radical, R<sup>8</sup> is hydrogen or a methyl radical, R<sup>9</sup> is hydrogen or a C<sub>1-3</sub>-alkyl radical, and R<sup>10</sup> is hydrogen, a C<sub>1-3</sub>-alkyl radical, a C<sub>1-3</sub>-alkoxy radical or a fluorine atom, or a pharmaceutically-acceptable, base addition salt of a compound of formula II wherein R<sup>9</sup> is hydrogen.

A particularly suitable value for R<sup>7</sup> is, for example, a methylthio or ethylthio radical, and a particularly suitable value for R<sup>9</sup> or R<sup>10</sup> when it is a C<sub>1-3</sub> alkyl radical is, for example, a methyl radical. A particularly suitable value for R<sup>10</sup> when it is a C<sub>1-3</sub> alkoxy radical is, for example, a methoxy radical.

A particularly suitable salt of a compound of formula II wherein R<sup>9</sup> is hydrogen is an alkali metal, alkaline earth metal, aluminium or ammonium salt, or a salt of an organic base affording a pharmaceutically-acceptable cation, for example triethanolamine.

Preferred compounds of the invention are those wherein R<sup>8</sup> is a methyl radical, R<sup>9</sup> is hydrogen, and R<sup>10</sup> is hydrogen or a methyl or methoxy radical or a fluorine atom.

Specific compounds of the invention are, for example, 5 - methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl) - indol - 3 - ylacetate acid, 5 - methoxy - 2 - methyl -

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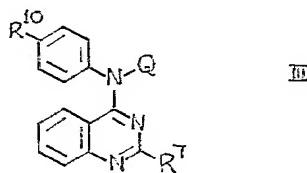
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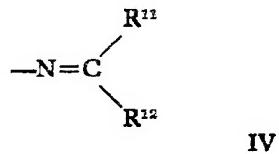
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- 1 - (2 - ethylthioquinazolin - 4 - yl)indol - 3 - ylactic acid, 2,5 - dimethyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylactic acid, 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylacetate.
- 5 A particularly preferred compound of the invention is 5 - methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl) - acetic acid.
- 10 The compounds of the invention may be obtained by the processes described in U.K. Patent Specification No. 1,356,834, but the following processes are particularly appropriate.

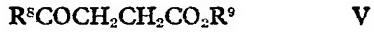
- 15 According to a further feature of the invention there is provided a process for the manufacture of a compound of the invention which comprises reacting a compound of the formula:—



- 20 25 wherein R<sup>7</sup> and R<sup>10</sup> have the meanings stated above and Q stands for an amino radical (—NH<sub>2</sub>) or a radical of the formula:—



- 30 wherein R<sup>11</sup> stands for hydrogen or a methyl radical, and R<sup>12</sup> stands for a methyl or phenyl radical, or an acid-addition salt thereof, for example a hydrochloride, with a compound of the formula:—



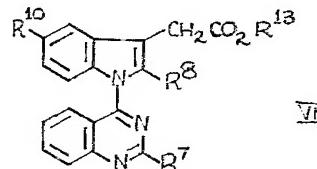
- 35 wherein R<sup>8</sup> and R<sup>9</sup> have the meanings stated above, under the influence of heat.

The reaction is preferably carried out at, for example 60 to 120° C., in the presence of an acid, for example hydrochloric acid and optionally in an excess of a low melting compound of formula V, for example laevulinic acid.

The starting material of formula III is obtained by the procedures described in U.K. 1,356,834.

According to a further feature of the invention there is provided a process for the

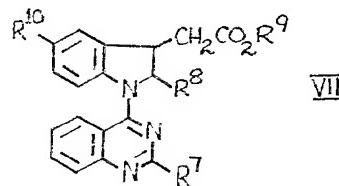
manufacture of a compound of the invention wherein R<sup>9</sup> stands for hydrogen, which comprises hydrolysing the corresponding ester of the formula:—



wherein R<sup>7</sup>, R<sup>8</sup> and R<sup>10</sup> have the meanings stated above, and R<sup>13</sup> is a C<sub>1-3</sub> alkyl radical.

A suitable hydrolytic agent is, for example, an alkali metal hydroxide, for example sodium hydroxide or potassium hydroxide. The hydrolysis is carried out in the presence of water, and optionally an organic solvent, for example ethanol, may be present. The reaction may be carried out at 50 to 150° C., for example at reflux temperature.

According to a further feature of the invention there is provided a process for the manufacture of a compound of the invention, which comprises dehydrogenating the corresponding indoline derivative of the formula:—



wherein R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> have the meanings stated above.

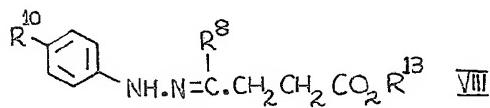
It is to be understood that by the word "dehydrogenating" there is meant the removal of one hydrogen atom from the 2-position, and one from the 3-position, of the said indoline derivative, so as to give the corresponding indole derivative. The dehydrogenation may be effected for example by means of a known compound having dehydrogenating properties, for example 2,3,5,6-tetrachloro - 1,4 - benzoquinone or 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone, in a suitable solvent, for example dry xylene, 1,2-dimethoxyethane or dimethylformamide, at 20 to 160° C., for example at reflux temperature. The indoline starting material of the formula VII may be obtained by using an analogous process to that described in United Kingdom patent specification No. 1,356,834 for the production of analogous starting materials.

According to a further feature of the invention there is provided a process for the manufacture of a compound of the invention

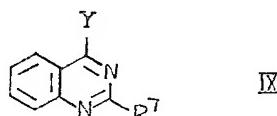
wherein R<sup>9</sup> is a C<sub>1-3</sub>-alkyl radical, which comprises esterifying the corresponding carboxylic acid of the formula II, wherein R<sup>9</sup> is hydrogen, or an acid halide or anhydride thereof, with an alcohol of the formula R<sup>13</sup>.OH, wherein R<sup>13</sup> has the meaning stated above.

The said esterification may be carried out by reacting the said carboxylic acid with the alcohol reactant, which may optionally be present in excess, in the presence of an acid, for example a Lewis acid, for example boron trifluoride etherate or methanolate, conveniently at 40 to 120° C., for example under reflux, or by any appropriate general method.

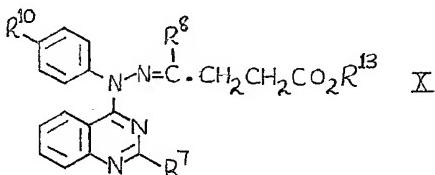
According to a further feature of the invention there is provided a process for the manufacture of a compound of the invention which comprises reacting a compound of the formula:



with a quinazoline derivative of the formula:



to give a compound of the formula:



and then ring closing the said compound of the formula X so as to give the desired product of the formula II, and wherein, R<sup>7</sup>, R<sup>9</sup>, R<sup>10</sup> and R<sup>13</sup> have the meanings stated above, and Y stands for a chlorine or bromine atom.

The process is carried out, and the intermediates are prepared, in an analogous manner to that described for the production of analogous compounds in United Kingdom patent specification No. 1,356,834.

The pharmaceutically-acceptable salts of the invention are obtained by conventional procedures.

The anti-inflammatory activity of the compounds of the invention has been demonstrated in two well known tests involving adjuvant induced arthritis and carrageenin induced oedema in the rat, their analgesic acti-

vity has been demonstrated in the so-called mouse squirm test.

Generally speaking the compounds of this invention show activity at a dose in the range 0.5 to 50 mg./kg. No toxic effects or undesirable side effects have been observed in the rat or mouse with the compounds of the invention, at doses at which the compounds show activity in the above mentioned tests.

When a compound of the invention is used as an anti-inflammatory or analgesic agent in the treatment of warm-blooded mammals, for example man, for example for the treatment of rheumatoid arthritis, it is recommended that said compound be administered orally at a total daily dose of 25 to 1000 mg. per 70 kg. bodyweight, for example as an aqueous or non-aqueous solution or suspension or as a dosage unit form, for example a tablet or capsule comprising 5 to 250 mg. of the said compound. Alternatively, the said compound may be dosed rectally as a suppository at a total daily dose of 25 to 1000 mg. per 70 kg. bodyweight, or it may be administered topically as necessary.

According to a further feature of the invention there is provided a pharmaceutical composition comprising a compound of the invention and an inert pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions may be in the form of, for example, dosage unit forms, for example tablets or capsules, or suppositories, aqueous or non-aqueous solutions or suspensions, sterile injectable aqueous or non-aqueous solutions, creams, lotions or ointments. The compositions are obtainable in a conventional manner using conventional diluents and carriers.

The pharmaceutical compositions of the invention may contain, in addition to a compound of the invention, at least one known agent having anti-inflammatory and/or analgesic activity, for example aspirin, acetaminophen, codeine, chloroquine, phenylbutazone, oxyphenbutazone, indomethacin, mefenamic acid, D-penicillamine, flufenamic acid, ibuprofen or an anti-inflammatory steroid, for example prednisolone. Those compositions intended for oral administration may, in addition, optionally contain at least one antacid, for example aluminium hydroxide, and/or a uricosuric agent, for example probenecid.

The invention is illustrated but not limited by the following Examples:

#### Example 1.

A mixture of acetaldehyde N<sup>1</sup> - (2-methylthioquinazolin - 4 - yl) - p - methoxyphenylhydrazone (3.5 g.), laevulinic acid (7.0 g.) and a saturated solution of dry hydrogen chloride in diethyl ether (10 ml.) was heated at 95—100° C. for 16 hours (the ether was allowed to evaporate). The dark brown reaction mixture was poured into water (600

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ml.) and the yellow brown solid which formed was collected by filtration, air-dried and triturated with methanol (30 ml.) to give 5-methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl) - indol - 3 - ylacetate acid as a yellow solid, which was crystallised from methanol to give crystalline material of m.p. 175-178°C.

The acetaldehyde hydrazone used as starting material was obtained as follows:-

A mixture of acetaldehyde *p*-methoxyphenylhydrazone (2.3 g.) and 4 - chloro-2 - methylthioquinazoline (2.9 g.) in dry 1,2-dimethoxyethane [30 ml.; dried over sodium aluminosilicate (molecular sieve type 4A; obtainable from BDH Chemicals Ltd., Poole, Dorset, England)] was heated under reflux for 15 minutes. The dark red syrup which deposited during the reaction was separated by decantation of the supernatant liquid. A fresh portion of dry 1,2-dimethoxyethane (30 ml.) was added, and the syrup was again separated by decantation. The residual solvent was re-

moved by evaporation to give acetaldehyde *N*<sup>1</sup>-(2 - methylthioquinazolin - 4 - yl) - *p*-methoxyphenylhydrazone hydrochloride as a thick syrup, of satisfactory purity by thin layer chromatographic analysis [silica gel; 50% ether: 50% petroleum ether (b.p. 40-60°C.)] and by NMR spectroscopy.

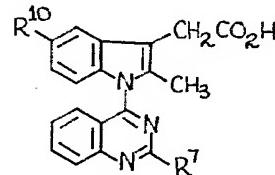
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### Example 2.

In a similar manner to that described in Example 1 the following compounds were obtained from the corresponding acetaldehyde hydrazone (or its hydrochloride)

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R <sup>7</sup>	R <sup>10</sup>	Characteristic Properties (m.p.)
ethylthio	methoxy	214-215°C
ethylthio	methyl	208-211°C
ethylthio	hydrogen	205-207°C

The acetaldehyde hydrazone derivatives used as starting materials for the indoles described in this Example, were obtained in a similar manner to that described in Example 1, except that if necessary, they were purified by chromatography on silica gel using as eluant, an increasing gradient of ether in petroleum ether (b.p. 40-60°C.).

2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylacetate as a pale yellow crystalline solid, m.p. 151-153°C.

The methyl 5 - methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylacetate used as starting material was obtained as follows:-

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A mixture of methyl 5 - methoxy - 2 - methylindolin - 3 - ylacetate (1.0 g.) and 4 - chloro - 2 - methylthioquinazoline (0.9 g.) in dry 1,2 - dimethoxyethane (35 ml.; dried over sodium aluminosilicate) was heated under reflux for 1 hr. The mixture was evaporated *in vacuo*, and the syrup residue partitioned between a saturated solution of sodium acetate (30 ml.) and chloroform (100 ml.). The chloroform extract was separated, dried over magnesium sulphate and evaporated. The dark red syrup obtained was purified by chromatography on a column of silica gel (180 g.), using initially a 1:3 v/v mixture and finally a 3:1 v/v mixture of ether and petroleum ether (b.p. 40-60°C.), to give methyl 5 - methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylacetate as a bright yellow syrup, pure by TLC [on silica gel, elution with 1:1 v/v ether and petroleum ether (b.p. 60-60°C.)]; NMR: 2-CH<sub>3</sub>, doublet at 8.84<sub>r</sub>; —SCH<sub>3</sub>, singlet at 7.8<sub>r</sub>.

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### Example 3.

A solution containing 2,3 - dichloro - 5,6-dicyano - 1,4 - benzoquinone (0.56 g.) and methyl 5 - methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl)indolin - 3 - ylacetate ((1.0 g.) in dry 1,2-dimethoxyethane [40 ml., dried over sodium aluminosilicate (molecular sieve type 4A; obtainable from BDH Chemicals Ltd., Poole, England)] was heated under reflux for 8 hrs. The mixture was concentrated *in vacuo* and the dark-coloured residue extracted with chloroform (3 x 50 ml.). The insoluble residue was removed by filtration through kieselguhr, and the filtrate evaporated *in vacuo*. The bright orange syrup thus obtained was purified by chromatography on a column of silica gel (180 g.) using a 1:3 v/v mixture of ether and petroleum ether (b.p. 40-60°C.) to give, after removal of solvents, methyl 5 - methoxy-

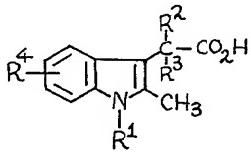
## Example 4.

A solution of methyl 5 - methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylacetate (1.2 g.) in propan - 2 - ol (20 ml.) was heated at 95° C. with a solution of sodium hydroxide (0.2 g.) in water (5 ml.) for 5 min. The orange solution was cooled to ambient temperature and acidified to pH 3 with formic acid. The mixture was evaporated to dryness *in vacuo*, and the residue recrystallised from methanol to give 5 - methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylacetic acid as a yellow, crystalline solid, m.p. 176 - 178° C.

## Example 5.

To a solution of 5 - methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylacetate (1.0 g.) in dry methanol was added boron trifluoride methanolate (0.5 ml.), and the dark coloured solution heated under reflux for 1 hr. Saturated sodium acetate solution (4 ml.) was added and the mixture was concentrated *in vacuo*. The residual orange oil was shaken with a mixture of water (50 ml.) and ethyl acetate (50 ml.), and the aqueous layer was separated. It was further extracted with ethyl acetate (2 × 30 ml.), and the extracts separated and washed successively with water (30 ml.) and saturated sodium chloride solution (30 ml.). After drying with magnesium sulphate, the extracts were evaporated, and the yellow residue obtained was crystallised from aqueous methanol to give methyl 5 - methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylacetate, as a pale yellow crystalline solid, m.p. 151 - 153° C.

We are aware of U.K. patent Specification No. 1,407,658, claim 1 of which claims a process for making compounds of the formula:

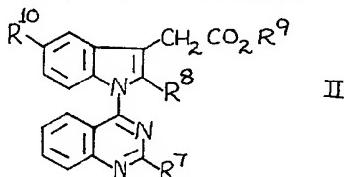


wherein R<sup>1</sup> stands for a quinazolin - 4 - yl radical which may optionally bear a C<sub>1-5</sub>-alkyl, C<sub>1-5</sub>-alkylthio or halogen substituent, and R<sup>2</sup> and R<sup>3</sup>, which may be the same or different, stand for hydrogen or a methyl radical, and R<sup>4</sup> stands for hydrogen or a C<sub>1-5</sub>-alkoxy or C<sub>1-5</sub>-alkyl radical, and pharmaceutically-acceptable salts thereof.

No claim is made in this Specification to any of the compounds defined in claim 1 of said U.K. patent Specification No. 1,407,658 whenever made by the process claimed therein.

Subject to the foregoing disclaimer WHAT WE CLAIM IS:—

1. A compound of the formula:—



wherein R<sup>7</sup> is a C<sub>1-3</sub>-alkylthio radical, R<sup>8</sup> is hydrogen or a methyl radical, R<sup>9</sup> is hydrogen or a C<sub>1-3</sub>-alkyl radical, and R<sup>10</sup> is hydrogen, a C<sub>1-3</sub>-alkyl radical, a C<sub>1-3</sub>-alkoxy radical or a fluorine atom, or a pharmaceutically-acceptable, base addition salt of a compound of formula II wherein R<sup>9</sup> is hydrogen.

2. A compound as claimed in claim 1 wherein R<sup>7</sup> is a methylthio or ethylthio radical, R<sup>8</sup> is hydrogen or a methyl radical, R<sup>9</sup> is hydrogen or a methyl radical, and R<sup>10</sup> is hydrogen, a methyl or methoxy radical or a fluorine atom.

3. A compound as claimed in claim 1 wherein R<sup>8</sup> is a methyl radical, R<sup>9</sup> is hydrogen, and R<sup>10</sup> is hydrogen, a methyl or methoxy radical or a fluorine atom.

4. The compound 5 - methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylacetate, or a pharmaceutically-acceptable base addition salt thereof.

5. The compound 5 - methoxy - 2 - methyl - 1 - (2 - ethylthioquinazolin - 4 - yl)indol - 3 - ylacetate, or a pharmaceutically-acceptable base addition salt thereof.

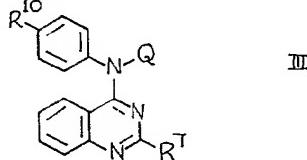
6. The compound 2,5 - dimethyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylacetate, or a pharmaceutically-acceptable base addition salt thereof.

7. The compound 2 - methyl 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylacetate, or a pharmaceutically-acceptable base addition salt thereof.

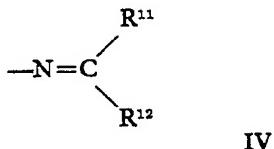
8. The compound methyl 5 - methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylacetate.

9. A pharmaceutically - acceptable base addition salt as claimed in any of claims 1 to 7 which is an alkali metal, alkaline earth metal, aluminium or ammonium salt, or a salt of an organic base affording a pharmaceutically-acceptable cation.

10. A process for the manufacture of a compound claimed in claim 1, which comprises reacting a compound of the formula:—



wherein R<sup>11</sup> is hydrogen or a methyl radical in claim 1 and Q is an amino radical or a radical of the formula:—

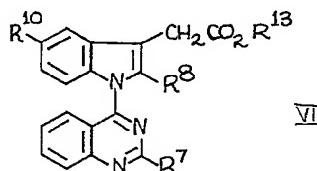


- 5 wherein R<sup>11</sup> is hydrogen or a methyl radical and R<sup>12</sup> is a methyl or phenyl radical, or an acid-addition salt thereof, with a compound of the formula:—



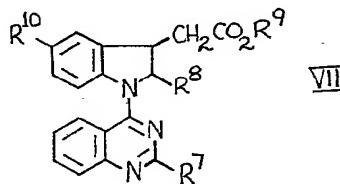
- 10 wherein R<sup>8</sup> and R<sup>9</sup> have the meanings stated in claim 1, under the influence of heat.

11. A process for the manufacture of a compound claimed in claim 1 wherein R<sup>9</sup> is hydrogen, which comprises hydrolysing the corresponding ester of the formula:—



wherein R<sup>7</sup>, R<sup>8</sup> and R<sup>10</sup> have the meanings stated in claim 1, and R<sup>13</sup> is a C<sub>1-3</sub>-alkyl radical.

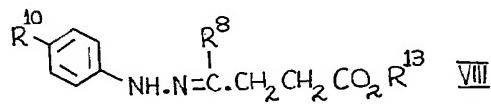
- 20 12. A process for the manufacture of a compound claimed in claim 1, which comprises dehydrogenating the corresponding indoline derivative of the formula:—



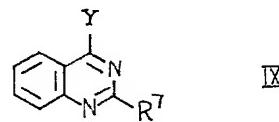
- 25 wherein R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, and R<sup>10</sup> have the meanings stated in claim 1.

- 30 13. A process for the manufacture of a compound claimed in claim 1 wherein R<sup>9</sup> is a C<sub>1-3</sub>-alkyl radical which comprises esterifying the corresponding carboxylic acid of formula II, wherein R<sup>9</sup> is hydrogen, or an acid halide or anhydride thereof with an alcohol of the formula R<sup>13</sup>.OH, wherein R<sup>13</sup> has the meaning stated in claim 11.

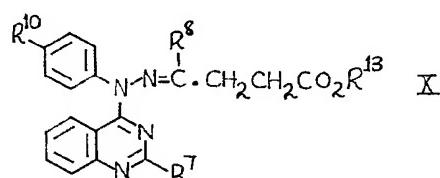
14. A process for the manufacture of a compound claimed in claim 1, which comprises reacting a compound of the formula:—



wherein R<sup>8</sup>, R<sup>10</sup>, and R<sup>13</sup> have the meanings stated in claim 11, with a quinazoline derivative of the formula:—



wherein R<sup>7</sup> has the meaning stated in claim 1 and Y is a chlorine or bromine atom, to give a compound of the formula:—



wherein R<sup>7</sup>, R<sup>8</sup>, R<sup>10</sup> and R<sup>13</sup> have the meanings stated above and then ring-closing the said compound of the formula X, under the influence of heat.

- 50 15. A pharmaceutical composition comprising a compound as claimed in claim 1, or a pharmaceutically-acceptable, base addition salt of such a compound wherein R<sup>9</sup> is hydrogen, and an inert pharmaceutically-acceptable diluent or carrier.

- 55 16. A pharmaceutical composition comprising 5 - methoxy - 2 - methyl - 1 - (2 - methylthioquinazolin - 4 - yl)indol - 3 - ylactic acid, or a pharmaceutically-acceptable base addition salt thereof, and an inert pharmaceutically-acceptable diluent or carrier.

- 60 17. A compound as claimed in claim 1, substantially as described in Example 1.

- 65 18. A compound as claimed in claim 1, substantially as described in any one of Examples 2 to 5.

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